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PTO/SB/21 (05-03)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	08/653,294
Filing Date	May 24, 1996
First Named Inventor	Carol A. CLAYBERGER
Art Unit	1644
Examiner Name	M. Dibrino
Total Number of Pages in This Submission: 39	Attorney Docket Number: 286002020023

ENCLOSURES (*check all that apply*)

- [x] Fee Transmittal Form + duplicate for Fee Processing (2 pages)
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to Group **(Appeal Notice, Brief, Reply Brief) Appellant's Brief in triplicate (36 pages)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please identify below):

Return postcard

Remarks

Customer No. 25225

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	MORRISON & FOERSTER LLP Laurie L. Hill - 51,804
Signature	Laurie L. Hill
Date	September 2, 2003

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV273019272US, in an envelope addressed to: Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 9-2-03 Signature: _____ (Michael Boyd)

sd-162773

PTO/SB/17 (05-03)
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FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 320.00

Complete if Known	
Application Number	08/653,294
Filing Date	May 24, 1996
First Named Inventor	Carol A. CLAYBERGER
Examiner Name	M. Dibrino
Art Unit	1644
Attorney Docket No.	286002020023

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account

Deposit Account Number: 03-1952

Deposit Account Name: Morrison & Foerster LLP

The Director is hereby authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		x		=	
Independent Claims		-3** =		x		=	
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	320.00
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37CFR 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 320.00

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	Laurie L. Hill	*Registration No. (Attorney/Agent)*	51,804	*Telephone*	(858) 720-7955
Signature				*Date*	September 2, 2003

sd-162772

Docket No.: 286002020023
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Carol A. CLAYBERGER, et al.

Application No.: 08/653,294 Group Art Unit: 1644

Filed: May 24, 1996 Examiner: M. Dibrino

For: IMMUNOMODULATING DIMERS

APPELLANT'S BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants hereby appeal from the final rejection of claims 2-4, 12, 13, 15-21, and 27, mailed December 30, 2002. A Notice of Appeal was filed along with a Petition for an Extension of Time on June 30, 2003. This Brief is believed to be timely filed on Tuesday, September 2, the next business day following the due date of Saturday, August 30, 2003. In accordance with 37 C.F.R. § 1.192, this Brief is filed in triplicate and is accompanied by the required fee. Appellants respectfully request that the rejection be reversed.

I. REAL PARTY IN INTEREST

The real parties in interest for this appeal are the assignee, the Board of Trustees of Leland Stanford Junior University, and the licensee, SangStat Medical Corporation. Appellants' assignment to Stanford University was recorded at Reel 8134 and Frame 0038 on September 11, 1996.

II. RELATED APPEALS AND INTERFERENCES

To appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 13 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 1, 5-11, 14, and 22-26

2. Claims withdrawn from consideration but not canceled: None

3. Claims pending: 2-4, 12, 13, 15-21, 27

4. Claims allowed: 15, 17[1]

5. Claims rejected: 2-4, 12, 13, 16, 18-21, 27

C. Claims On Appeal

The claims on appeal are claims 2-4, 12, 13, 16, 18-21, and 27.

[1] Pending updated interference search. *See* Paper No. 60.

IV. STATUS OF AMENDMENTS

Appellants filed an Amendment After Final Rejection on May 30, 2003. Appellants gratefully acknowledge the Examiner's entry of the proposed claim amendments per the voicemail left by the Examiner on August 24, 2003 and the Advisory Action mailed August 27, 2003 (Paper No. 60), the indication that the objections and rejections under 35 U.S.C. § 112, first and second paragraph are overcome, and the notice of allowable subject matter in claims 15 and 17. Accordingly, the claims presented in Exhibit A include the amendments proposed in the Amendment submitted under 37 C.F.R. § 1.116 on May 30, 2003.

Appellants note that claim 16 does not appear on the list of pending claims in Paper No. 60, but it has not been canceled by Appellants or the Office. Therefore, claim 16 is still pending and, according to the Advisory Action, has no rejections indicated against it.

V. SUMMARY OF INVENTION

Prior art formulations for peptide immunomodulation of undesirable cytotoxic T lymphocyte ("CTL") activity have been based on the use of monomers of HLA class I peptides alone or in combination with peptides from unrelated molecules, *e.g.*, cytokine peptides. The present invention represents a different approach in that HLA peptide dimers, rather than monomers, are employed as the active ingredient in the immunomodulating composition.

Generally, the peptides comprise amino acid sequences related to a Class I HLA-B α1-domain. *See* page 3, lines 8-10. These peptides interact with CTLs to inhibit the cytotoxic activity against a target cell. In this way, the peptides modulate an ongoing immune response. Such immunomodulation is particularly desirable in patients with autoimmune disease or organ transplants. Typically, the systemic immunosuppressive agents used to treat autoimmune disease or transplant rejection are non-specific, and therefore debilitate all immune responses, leaving the patient susceptible to infection. The immunomodulating peptides of the instant invention offer a

specific immunosuppressive agent that preferentially targets the undesirable immune activity, *i.e.*, CTL activity, while leaving other components of the immune response intact. *See, e.g.*, page 1, lines 18-25.

Thus, the invention of claims 2-4, 12, 13, 18-21, and 27 are directed to compositions of Class I HLA-B α1-domain peptides of tandem homodimers, inverted homodimers, or heterodimers that immunomodulate T cell response by inhibiting the lytic activity of CTLs. *See* page 3, line 7 to page 4, line 5. Claims 18-20 further define methods of use for the claimed compositions in a transplant recipient.

VI. ISSUES

Only one issue is presented for review:

Whether the claimed compositions and methods are obvious under 35 U.S.C. § 103 (a) over Olsson, U.S. Patent No. 5,073,540, or Krensky, WO 88/05784.

VII. GROUPING OF CLAIMS

The inventive concept of all claims is the same and all claims may be considered together for the purposes of the rejection under 35 U.S.C. § 103 (a).

VIII. ARGUMENTS

It is believed that the sole issue on appeal should be resolved in favor of the appellants because neither Olsson nor Krensky render the claimed compositions and methods obvious.

Claims 2-4, 12, 13, 18-21, and 27 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Olsson, U.S. Patent No. 5,073,540, or Krensky, WO 88/05784, for reasons of record. *See* Paper No. 57, pages 3-4, Paper No. 38, page 3, and Paper No. 29, page 3. To summarize, the Office asserts that Olsson discloses compounds with "essentially the same structure"

as the instant application. The Office further asserts that Krensky also discloses similar peptides and the use of conventional techniques to extend the half-lives of those peptides. Moreover, the Office takes the position that a skilled artisan would expect dimers of the same unit to exert the same functional effects as a monomer. Appellants assert that this rejection is in error.

A. The legal standard of the nonobviousness requirement

A *prima facie* case of obviousness requires the satisfaction of three requirements. First, the reference must teach or suggest all of the claim limitations. Second, a suggestion or motivation to modify the teachings of the reference to result in the claimed compositions and methods much be found either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. Third, the reference must provide a reasonable expectation of success for such a modification. *Manual of Patent Examination Procedure* (hereinafter "MPEP") § 2142 (8th ed. 2001).

More specifically, the obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Any disclosure teaching away from the claimed invention must be considered in the obviousness analysis. MPEP § 2142.01. The fact that an invention can be modified is insufficient to establish *prima facie* obviousness in the absence of a suggestion or motivation to make such a modification. *Id.* Furthermore, if a modification changes the principle of operation of a reference, the teachings of that reference do not render the claimed invention obvious. *Id.* Finally, in the analysis of prior art references, it is improper to exercise hindsight to select bits and pieces from the

references to create a motivation to modify that is not found in the references, but only in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Appellants respectfully submit that a *prima facie* case for obviousness has not been presented. The claimed compositions relate to homodimeric and heterodimeric peptides comprising HLA-B α1 domain sequences that inhibit cytotoxicity. Therefore, a *prima facie* case of obviousness requires that (1) the reference teach or suggest dimeric peptides of HLA-B α1 domain sequences that are inhibitory to cytotoxicity or (2) the references provide a motivation to modify the teachings of the reference to result in the claimed compositions, as well as a reasonable expectation of success in such a modification. MPEP § 2142 (8th ed. 2001). For the reasons discussed below, the cited references fail to fulfill these requirements for *prima facie* obviousness.

B. Olsson fails not render the claimed compositions and methods obvious

Olsson fails to render the claimed compositions and methods obvious because Olsson fails to teach or suggest the claimed compositions of peptide dimers comprising amino acid sequences related to Class I HLA-B α1 domain that modulate CTL activity and methods of use thereof. Olsson discloses the use of dimeric peptide compositions that are clearly distinguishable from the instant peptide dimers. Olsson's dimers comprise two peptide sequences that bind two different sites. One peptide sequence is from a Class I MHC molecule, but the second peptide sequence is one that binds the binding site of a second cell surface receptor molecule, *e.g.*, a ligand peptide. *See* column 2, lines 29-35. Olsson's second cell surface receptor is disclosed as including endocrine, paracrine, and autocrine receptors, adrenergic receptors, lipoprotein receptors, opiate receptors, and steroid receptors. *See* column 2, line 49 to column 3, line 4. In other words, Olsson's invention lies in peptide dimers comprising a Class I MHC peptide as well as a peptide that binds the binding site of a second cell surface receptor, a fundamentally different peptide than that of the instant application. *See, e.g.*, Claim 1. The design of Olsson's peptide dimers conveys to one of skill in the art the requirement of two distinct interactions in order to modulate the immune response.

Presumably, such modulation can be in the form of antagonist, *e.g.*, blocking a signal necessary for eliciting CTL activity from the T cell, or in the form of an agonist, *e.g.*, sending a "negative" signal that interrupts or subverts the signal necessary for the CTL response. Regardless of the exact molecular mechanism, the design of Olsson's peptides teaches that at least two distinct peptides are involved. Olsson does not describe or suggest dimeric peptide comprising only Class I MHC peptide sequences that bind the cell surface receptor through non-binding site interactions. Because Olsson's dimeric peptides require a peptide that binds the binding sites of a cell surface receptor as well as a Class I MHC peptide, they are clearly distinguishable from the dimeric peptides of the instant application that bind through non-binding site interactions alone. Therefore, the definitive element of the claimed invention - dimeric peptides comprised only of Class I MHC sequences - is clearly distinguishable from Olsson.

Olsson fails to provide any motivation to modify its teachings to result in the compositions and methods of the instant claims. First, Olsson lacks any express or inherent teaching regarding the desirability of modifying its peptides to result in the instant dimeric peptides. Olsson's teachings are limited to the desirability of peptide dimers that include a Class I MHC peptide and a peptide that binds the binding site of a cell surface receptor. Second, Olsson actually teaches away from modifying his invention to create peptide dimers of Class I MHC sequences by teaching that the desirable dimer contains peptide sequences from Class I MHC and a peptide that binds the binding site of a cell surface receptor.

Olsson provides no reasonable expectation of success for a modification of its teachings to result in dimeric peptides of only Class I MHC sequences. Olsson discloses only the desirability of a dimeric peptide that binds the binding site of a receptor and an allosteric site through the Class I MHC peptide. Because Olsson teaches away from the desirability of using a peptide that binds a receptor only through non-binding site interactions, Olsson provides no reasonable expectation of

success regarding the modification of its dimeric peptides to result in the instant dimeric peptide of Class I MHC sequences that bind a receptor through non-binding site interactions.

Finally, modifying Olsson's dimeric peptides to result in the instant dimeric peptides changes the principle of operation for the Olsson invention, and therefore does not render the claimed compositions and methods obvious. MPEP § 2143.01 ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the reference are not sufficient to render the claims prima facie obvious."). As discussed *supra*, Olsson's peptides require binding of the binding site of a cell surface receptor. *See, e.g.*, Claim 1. As the Olsson peptides are believed to modulate cell signaling, the requirement for a peptide binding the binding site of a cell surface receptor appears to be a critical element of the invention. It is in this way that the Olsson peptides target specific interactions for modulation. *See, e.g.*, Column 2, lines 38-44. Therefore, in the absence of a teaching or suggestion to the contrary, a person of ordinary skill in the art would not have modified the teachings of Olsson to create dimeric peptides of the instant application because such a modification would eliminate a critical element of the Olsson peptides.

Hence, the disclosure of Olsson fails to establish *prima facie* obviousness.

C. Krensky fails to render the claimed compositions and methods obvious

Krensky fails to render the compositions and methods of the instant application obvious because Krensky does not teach or suggest dimeric peptides comprising Class I MHC sequences. Rather Krensky discloses only the use of monomeric peptide comprising only Class I MHC sequences. Moreover, Krensky fails to teach or suggest that it is desirable to modify the disclosed monomeric peptides to result in the dimeric peptides of the instant application. In the complete absence of such teaching or suggestion to modify the disclosed peptide, Krensky cannot provide motivation or a reasonable expectation for success for such modification. Therefore, Krensky does not establish *prima facie* obviousness.

Appellants respectfully submit that there must be some clear evidence to establish why the modification would have been obvious which can properly qualify as prior art. *In re Kaplan*, 229 U.S.P.Q.2d 678, 683 (Fed. Cir. 1986). The Office is required to provide more than a mere assertion that the acknowledged differences between the cited references and the claimed subject matter would have been obvious to the skilled artisan. If the rejection is only based upon facts within the personal knowledge of the Examiner and such facts must be supported by an affidavit from the Examiner in accordance with 37 C.F.R. 1.104(d)(2). This appears to be the case here. Accordingly, Applicants again respectfully request an affidavit from the Examiner if the Office maintains the argument that dimers of the same unit have the same effect as that of the monomer.

Moreover, the dimeric peptides have unexpected superior properties and therefore are not obvious to the skilled artisan. The Office asserts that the skilled artisan would expect dimers of the same unit to exert the same functional effects as a monomer, and therefore the disclosure of Krensky allegedly renders the claimed compositions and methods obvious. Appellants respectfully submit that the unexpected superiority of the dimeric peptide relative to the monomeric peptides of Krensky renders the claimed compositions nonobvious. *See In re Soni*, 34 U.S.P.Q.2d 1684 (Fed. Cir. 1995) (holding that what is unexpected to the skilled artisan is not obvious). Objective evidence disclosed in the instant specification demonstrates the unexpected superior inhibitory effects of dimeric peptides on CTL activity. Specifically, Appellants disclose the results of actual experiments performed with peptide monomers and dimers of Class I MHC sequences on page 22 of the specification, lines 1-9. The experiments can be summarized as follows: While the monomers reduced CTL activity, the inverted dimer B2702.84-75/75-84 and the homodimer B2702.75-84/75-84 were unexpectedly superior to the monomer in their ability to completely inhibit cytotoxicity. *See* specification, at page 22, lines 5-9. In other words, the evidence demonstrates that monomers do not exert the same inhibitory effect as dimers of the same unit on CTL activity because the monomers exerted only a partial inhibitory effect. Appellants respectfully submit this objective

evidence disclosed in the specification demonstrates the unexpected superiority of the dimeric peptides relative to the monomeric peptides, and therefore the dimeric peptides are nonobvious in view of Krensky.

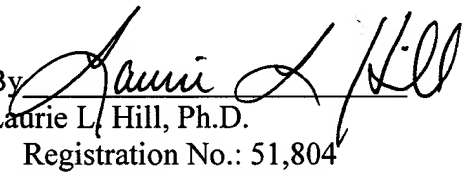
In light of the above remarks, Applicant respectfully submits that the rejection under 35 U.S.C. § 103(a) is overcome. Therefore, Applicants request the withdrawal of this rejection.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A do include the amendments filed by Applicant on May 30, 2003.

Dated: September 2, 2003

Respectfully submitted,

By 

Laurie L. Hill, Ph.D.
Registration No.: 51,804
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130

(858) 720-7955

APPENDIX A

Claims Involved in the Appeal of Application Serial No. 08/653,294

Claim 2 (Previously presented): The peptide of claim 27 wherein aa^{80} is I.

Claim 3 (Previously presented): The peptide of claim 27 wherein at least one of the amino acids is the D-isomer.

Claim 4 (Previously presented): The peptide of claim 3 wherein all of the amino acids are the D-isomer.

Claim 12 (Previously presented): The peptide of claim 27 wherein aa^{82} is L.

Claim 13 (Previously presented): The peptide of claim 27 wherein aa^{83} is R.

Claim 15 (Previously presented): A peptide dimer that inhibits cytotoxicity wherein said peptide dimer comprises RIALRYYRLAIR (SEQ ID NO:40), YRLAIRRIALRY (SEQ ID NO:36), RIALRYRILLRY (SEQ ID NO:41) or YRLLIRYRLAIR (SEQ ID NO:42).

Claim 16 (Previously presented): The peptide of claim 27 which is YRLAIRLNERRENLRIALRY (SEQ ID NO:26) or YRLAIRLNERYRLAIRLNER (SEQ ID NO:31).

Claim 17 (Previously presented): The peptide dimer of claim 15 which is YRLAIRRIALRY (SEQ ID NO:36).

Claim 18 (Previously presented): A method for extending the period of acceptance by a recipient of a transplant from an allogeneic or xenogeneic MHC donor, said method comprising:

administering to said donor in accordance with a therapeutically effective regimen and in an amount effective to extend the period of acceptance of said transplant, the peptide of claim 27; whereby the period of acceptance of said transplant is extended.

Claim 19 (Previously presented): The method of claim 18, wherein said compound is administered in combination with a subtherapeutic dosage of an immunosuppressant, and said period of acceptance is extended as compared to the period which would have resulted from the administering of said immunosuppressant as said subtherapeutic dosage in the absence of said peptide.

Claim 20 (Previously presented): A composition comprising the peptide of claim 27 and a subtherapeutic dosage of an immunosuppressant, together in an amount sufficient to inhibit transplant rejection in a mammal, in a physiologically acceptable medium.

Claim 21 (Previously presented): The peptide-type compound of claim 27 which is a peptide and wherein all the amino acid residues in said peptide are gene-encoded.

Claim 27 (Previously presented): A peptide dimer that inhibits cytotoxicity and consists of up to 60 amino acids, and comprises one of the following sequences:

R E aa^{77} L R aa^{80-83} Y (I) (SEQ ID NO:38) or

Y aa^{83-80} R L aa^{77} E R (II) (SEQ ID NO:39), and

N-terminal acylated and/or C-terminal amidated or esterified forms;

wherein:

aa^{77} is D, S or N;

aa^{80} is I or N;

aa^{81} is A or L;

aa^{82} is R or L;

aa^{83} is G or R.